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EPA SAP on Benzo[a]pyrene (BaP

Charge questions to Panel:

Literature search/study selection. Is the literature search strategy well documented? Please identify additional peer-reviewed studies that might have been missed.

RESPONSE
The EPA literature search is thorough, well-documented, and comprehensive. In my own search I identified a few additional articles that may provide some relevant information. These are:

Perera et al. (2014) on PAH exposure and ADHD in children (Perera et al., 2014) and two experiments in animals. One by Patri et al. on BaP in developing rats on learning and the role of NA as a potential protective factor (Patri et al., 2013) and one on BaP in adult rats on motor and cognitive behavior (Maciel et al., 2014), although the latter is less relevant to developmental neurotoxicity.

2. **Hazard identification.** In section 1, the draft assessment evaluates the available human, animal, and mechanistic studies to identify the types of toxicity that can be credibly associated with benzo[a]pyrene exposure. The draft assessment uses EPA's guidance documents (see http://www.epa.gov/iris/backgrd.html/) to reach the following conclusions.

Hazard identification will be discussed later.

2a. **Developmental toxicity** (sections 1.1.1, 1.2.1). The draft assessment concludes that developmental toxicity and developmental neurotoxicity are human hazards of benzo[a]pyrene exposure. Do the available human and animal studies support this conclusion?

RESPONSE
The focus of my preliminary comments will be on the developmental neurotoxicity animal data. There are a series of relevant human epidemiological studies which will also be considered, including, but not limited to: (Perera et al., 2012b;Perera et al., 2011;Tang et al., 2006;Perera et al., 2005;Perera et al., 2004;Tang et al., 2008;Perera et al., 2012a;Perera et al., 2009).

Descriptions of the key animal experiment about BaP are summarized in the EPA Toxicological Report and will not be repeated here. Here the focus will be on the strengths and weaknesses of these studies.

Tang et al. (Tang et al., 2011) treated Wistar rats starting at weaning for 14 weeks with 1, 2.5, or 6.25 mg/kg BaP i.p. from approximately P21-218 and assessed the animals in the Morris water maze (MWM) to a hidden platform as a test of spatial learning starting one day after the end of treatment. In this procedure rats were tested in a circular pool 180 cm in diameter and

apparently given 1 trial/day although the authors do not specific this parameter and it may have been several trials per day. They found significant increases in maze latency on all 5 days of testing in the 2.5 and 6.25 mg/kg BaP dose groups but only on day-3 in the 1 mg/kg dose group. They gave a reference memory (probe) trial after the last learning trial on day-5. On this trial, they found effects of BaP at all doses on platform site crossovers and they found reductions in target quadrant bias in the 2.5 and 6.25 mg/kg BaP dose groups. **Strengths**: They tested multiple doses, groups sizes (9/group) were minimally adequate, the maze was appropriately sized for rats, reasonable learning curves were obtained, and the data appropriately analyzed. **Weaknesses**: Latency is a potentially confounded index of learning if performance, such as swim speed, is affected by the independent variable, an issue the authors fail to address. Also, the probe trial was given shortly after the last learning trial therefore it cannot be determined if the effects were on working or reference memory (the probe trial should have been given 24 h or more hours later). Also the probe trial was too long at 120 s; it is known that spatial bias progressively deteriorates after 30 s. This is mitigated by the fact that the effects of BaP were significant even with a longer than optimal probe trial. More importantly, while treatment began on approximately P21, this was not an early but rather a late developmental exposure period that extended well into adulthood. Moreover, it is not clear that the effects were irreversible since testing commenced shortly after the last treatment rather than allowing for a no-treatment period to intervene between the end of treatment and testing in order to determine the permanence of the effects observed.

Qiu et al. (Qiu et al., 2011), similarly to Tang et al. (2011) above, gave Sprague-Dawley male rats 6.25 mg/kg BaP i.p. but in this study they used P28 rats and treated them for 14 weeks. Rats were tested an unspecified number of days after the last treatment in a smaller 130 cm diameter MWM with a 9 cm hidden platform. They gave 4 trials/day from different start locations for 5 days following a habituation day in the pool with no platform present as acclimation. Apparently the probe trial was given on the last day of learning trials. They found a significant increase in latency to find the platform across all 5 days of testing and a reduction in the number of platform site crossovers and time spent in the target quadrant on the probe trial. **Strengths**: They used 8 rats/group, a minimally sufficient sample size, the data were appropriately analyzed, and the MWM procedures were generally appropriate (with some caveats). **Weaknesses**: A 130 cm maze for adult male SD rats is too small to provide a sufficient test of spatial navigation. Adult rats should be assessed in mazes no less than 183 cm (6 ft.) in diameter. Probe trials should be given 24 h or more hours after the last learning trial, and latency is a potentially confounded index of learning and should be cross-validated against swim speed and/or analysis of path length, neither of which were reported in this experiment. But the greatest concern about this study is that the BaP and Control groups differed significantly on Day-1 of MWM testing. This raises the concern that the BaP animals started out the test performing differently. It is a fundamental concept in learning and memory that if groups start out different they are likely to be different because of a performance difference unrelated to learning. This can be resolved by examining the trials on day-1 individually. Ideally, both groups start out the same on trial-1 when none of the animals know where to go to find the platform. If the groups begin to diverge on trials it after the first or second it suggests that the treated animals are less able to find and/or remember where the platform is after having found it the first few times but if they start out not being able to find it as well as controls, then one has to consider that they may have impaired swimming ability or vision and therefore have secondary sensorimotor impairments that reduce their ability to perform the spatial aspects of the task. Unfortunately, the authors did not address this issue thereby leaving it unresolved. This experiment is also not a test of early, but rather of late, developmental effects.

Xia et al. (Xia et al., 2011) like Qiu et al. (2011) above used male SD rats and started treatment at P28 and treated for 13 rather than 14 weeks. They used 8 rats/group and the dose groups were Control, 1, 2.5, and 6.25 mg/kg BaP given daily by i.p. injection dissolved in DMSO and diluted with corn oil. In this experiment, rats were tested in the MWM before BaP treatment (where no group differences were found) and after the end of treatment. This maze was also 130 cm in diameter and platform size was unspecified. For the post-treatment MWM assessment, rats were given 4 trials per day for 5 days with a probe trial given shortly after the last learning trial on day-5. Significant increases in escape latencies were found in the 2.5 and 6.25 mg/kg BaP groups and as in the Qiu et al. study, the effects were uniform on all days including day-1, again raising concern about swim speed or other interfering performance effects of the compound such that the animals in the treated groups may not have started the test equally capable of performing it. On the probe trial, an effect of 6.25 mg/kg BaP dose was found on platform site crossovers and on time in the target quadrant. Standard control methods to rule-out possible sensorimotor deficits are to conduct separate cued trials with a visible platform with curtains closed around the maze to prevent use of distal cues, to track swim speed during learning trials, and to report path length, which is largely immune from speed effects. Strengths: The study has minimally sufficient sample sizes, it included 3 BaP doses levels and two controls groups (vehicle and what they refer to as 0 mg/kg), the data were appropriately analyzed, and the effects at the two higher doses were clear-cut. Weaknesses: As in several of the above studies, concerns exist about the small size of the maze for adult male rats, the reliance exclusively on latency without convergent measures less prone to confounding, the differences on day-1 of the test with no analysis of day-1 data trial-by-trial, and the fact that the probe trial was not given 24 h or more after the last learning trial.

Chen et al. (Chen et al., 2012) appears to be one of the strongest studies on BaP during early development. They mated SD rats in-house and culled litters to 8 (4 M and 4 F), randomized pups several times among dams with the goal of distributing and thereby hopefully neutralizing litter effects, they used 40 litters in the experiment with 10 males and 10 females from different litters for testing. Progeny were treated with 0.02, 0.2, or 2 mg/kg BaP by gavage on P5-11 and the offspring tested for landmark development on P12, 14, 16, and 18, and at later ages in an open-field, elevated plus maze (EPM), and MWM, the later at two ages, P35 and again at P70. Most of the behavioral tests were standard but the MWM requires examination because details matter greatly on this test. The pool was 130 cm in diameter with a 9 cm platform. On day-1 rats were given a 60 s trial with no platform as habituation/acclimation; no measurements were taken. Spatial learning occurred on the following 4 days with 4 trials/day with an ITI of 5 min. On day-5 rats received a 60 s probe trial with the platform removed after the last learning trial was given on day-5. Modest but significant body weight reductions were seen on P36 and 71 in the 2 mg/kg group but none of the physical landmarks of development were affected. There were delays in surface righting in the low, mid and high dose groups but on different days; there were delays in the inclined surface test (incorrectly call negative geotaxis) at all doses on P12 and only in the high dose on P14. In the open-field there were increases in activity and rearing at P34 and 69 but not at P18 or P20, and these effects were mostly in the high dose group with one effect at P69 in the mid dose group on activity but not on rearing. There were also effects in the EPM at P70 with increased time in open, reduced latency to first open entry, increased number of open arm entries, and decreased entries into closed arms; these effects were seen in the 0.2 and 2 mg/kg BaP groups for latency and time in open at P70 but not at P35. On the third measure, number of open arm entries, there were increases at P70 in the 2 mg/kg males and in the 0.2 and 2 mg/kg group females. The fourth measure was number of closed arm entries and complimentary to open arm entries and does not provide unique information. The effects were more prominent in the high dose group than in the mid dose group with no effects in the low dose group on the EPM test. But by far the most striking finding in this study was in

the MWM. In both males and females, and at both P36-39 and P71-74, escape latencies to find the hidden platform were markedly longer in the high dose group than in Controls or the low dose group. At the adult age, there were also significant latency increase found in the mid dose group. On the probe trial, in both males and females at P40 and P75 time in the target quadrant and number of site crossovers were significantly reduced in the high dose group at both ages, and in adults also in the mid dose group. **Strengths**: This study has a number of strengths; these included the care to use in-house breeding, standardizing litter size, balancing for sex, testing multiple dose levels of BaP, administering BaP by gavage rather than by i.p injection, efforts to neutralize litter effects, use of multiple behavioral tests, appropriate statistical analyses of the data (see one caveat), and use of acceptable (if not optimal) MWM procedures. **Weaknesses**: Despite these strengths, the study has weaknesses many of which are described above for other studies. The size of the MWM, while appropriate for the P36-39 rats, was undersized for adult rats. Mitigating this is the fact that BaP-related effects were seen despite the small size of the maze. Another concern is the reliance on latency as the sole index of performance under the presumption that it accurately reflects learning when it may not, an issue of increased concern inasmuch as fact that in all groups the affected BaP animals showed marked latency differences on day-1. No sub-analysis of each trial on day-1 was performed to determine if the groups start out equally. In addition, no cued trials were given to rule-out visual problems. No measurements of path length or swim speed were recorded to rule-out other potential performance factors, and the probe trial was given immediately after the last learning trial thereby limiting its interpretive value. The use of the LSD a posteriori test is inappropriate. This test over-calls significant differences when there are more than three groups, as there were in this experiment, because it does not control for multiple comparisons. Had an appropriate a posteriori pairwise comparison been used, such as the Hochberg step-up method, or the False Discovery Rate method, some of the smaller group differences reported as significant might not have been by other methods. In the EPA review of this study, the parallelism of the learning curves was also discussed. It was noted that this reflected equal learning in all groups, which is correct. Only if we knew the individual performance on the 4 trials on day-1 could it be determined if the groups began the test equally or if the BaP groups were different from the outset. The EPA review also expressed concern about the interpretative value of the probe trial data in light of the fact that the affected BaP groups never reached the same level of proficiency on the learning trials as Controls, suggesting that they had not learned the platform's location sufficiently to be able to remember it as well as Controls on the probe trial. This concern is also valid. For the reasons identified by the EPA and for the additional reasons identified herein, the MWM data in this study are not sufficient for determining a POD (point of departure).

Li et al. (Li et al., 2012) conducted an experiment using an inbred mouse strain with a Loss of Function (LOF) mutation in the Cpr gene which encodes for the P450 enzyme oxidoreductase which is involved in BaP metabolism. This is a specialized experiment to test a specific hypothesis. It is of interest because the KO and WT mice were given BaP on E14-17. BaP was administered by inhalation at a dose of 100 g/m^3. Of particular interest in terms of developmental neurotoxicity was that among other parameters assessed in the offspring, mice were tested on an object discrimination task which was a modified version of the better known Novel Object Recognition test (NOR). Setting the details aside at present, the upshot was that the BaP-exposed KO mice, but not BaP-exposed WT mice, showed a marked reduction in novel object preference suggesting a hippocampally-mediated non-spatial learning deficit. Because the effect occurred only in the KO mice that were deficient in metabolizing BaP, the data suggest that BaP is more toxic in those with reduced oxidoreductase capacity. In humans this could occur by interindividual CNV or SNP differences causing some to be more susceptible to BaP than others. Unfortunately, only 4-5 mice were tested per group in a test known for its variability and replication problems. This reduces confidence that the effect is valid.

Bouayed et al. (Bouayed et al., 2009) also used mice. In this experiment Swiss albino mice were treated with 0, 2 or 20 mg/kg BaP by gavage on P0-14 and developmental parameters and behavior assessed at different ages. Assessments included physical development, maternal behavior (nest building and pup retrieval), surface righting, inclined plane (a.k.a. negative geotaxis), forelimb grip suspension; open-field on P15, water escape pole climbing on P20, EPM on P32, and spontaneous alternation on P40. No effects of BaP were found on physical development or maternal behavior. Delays in surface righting were found in both BaP groups on P3 and 5, on inclined plane in the high dose group on P5, 7, and 9, on the wire suspension test on P9 and 11, with no effects in the open-field, delays in males in the high dose group on the water escape test, and increased time in open and related measures in the EPM. One low dose effect was also seen in as increased alternation frequency in the Y-maze, an effect not seen at the dose 10 times higher. Strengths: This is one of the few developmental neurotoxicity experiments in mice and offers a slightly different species perspective. The study also included testing more than one dose of BaP, multiple behavioral tests, and appropriate statistical analyses. Weaknesses: Only 5 litters were used in each group and there is no evidence that litter effects were accounted for. Many of the tests, while affected, are of limited interpretative value because they may represent transient delays from which full recover my occur, and the doses of BaP are high.

In a study not included in the EPA review is by Maciel et al. (Maciel et al., 2014) motor and cognitive effects were assess in Wistar rats. However, this study's relevance to the current assessment is marginal since the exposure was in adult rats.

More relevant is a study not included in the EPA review by Patri et al. (Patri et al., 2013). In this unusual design, P5 Wistar rats were given a single intracisternal injection of 0.1 μM of BaP. The rats were raised and tested in a MWM before 6 weeks of age. Starting on P28, rats were tested in a 143 cm diameter maze for 8 days, 4 trials/day with a probe trial given 24 h after the last learning trial. The BaP group had significantly longer escape latencies than untreated or vehicle treated controls on days 3-8. Significantly, not only were the treated group's latencies longer, they had much longer path lengths than controls. Furthermore, swim speed was assessed and no differences found. On the probe trial, the BaP groups has fewer site crossovers and reduced time in the target quadrant. Strengths: This experiment conducted the MWM better than in any of the above studies because they appropriately accounted for and eliminated concerns over potential swim speed differences by directly measuring swim speed and by analyzing path length. They also showed that the groups began the test with essentially identical performance. They also conducted the probe trial 24 h after the last learning trial, making a reference memory deficit apparent without confounding with possible working memory effects. Weaknesses: The intracisternal route of BaP administration makes this study difficult to utilize to compare to anything else. In addition, the groups sizes were marginal: N = 4 in the untreated group, N = 7 in the DMSO vehicle group, and N = 8 in the BaP group. In addition, it is not stated how many litters these rats came from leaving open concern that they may have been drawn from a small number of litters without attention to proper litter sampling.

Preliminary Synthesis: The above developmental neurobehavioral studies on provide reasonable evidence that BaP induces developmental neurotoxicity in animals. Several of the studies are fairly well done and provide reasonable evidence of neurotoxicity. Nevertheless, each of the studies has limitations and some of these are significant. This applies especially to some tests with known experiment-to-experiment and cross-laboratory variability. These include the EPM and NOR tests. Studies using these methods should be replicated by the lab and ideally by another lab where similar effects are found before significant weight should be

placed on these findings. There are many examples in the literature where findings with these tests cannot be replicated. Methods such as the open-field test of locomotor activity are more reliable provided the test is properly done. This includes using an automated system, testing for a sufficient length of time (30-60 min, rather than 5 min), and proper environmental controls. The MWM has been heavily represented in the above experiments, largely in the absence of other tests of learning and memory. While the MWM is a superb test when properly conducted to assess spatial learning and reference memory, and is a strongly hippocampally-dependent form of cognition that should be assessed, it is unfortunate that the above datasets do not have the benefit of convergence by having other learning and memory tests use to cross-validate the MWM findings. Conversely, the fact that there are multiple experiments using the MWM increases the confidence that developmental BaP has effects on spatial learning and memory, and this is a definite strength this set of experiments taken as a whole. More significantly, however, are deficiencies in the MWM methods in every experiment reviewed. This raises concern about how much weight should be placed on these data. The caveats are not trivial. Failure to include proper maze scaling, and most importantly control for potential confounding for non-cognitive performance factors casts considerable doubt on these data. Why these experiments have not attended to such concerns is unclear but as they stand, considerable doubt cannot be avoided when analyzing their the value of their findings. A further limitation is that not one of the above studies included a reversal learning phase in their MWM procedures. This can be a valuable method for providing additional evidence that the acquisition deficits are sufficient to carryover to reversal or became even larger.

2b. **Reproductive toxicity** (sections 1.1.2, 1.2.1). The draft assessment concludes that male and female reproductive effects are a human hazard of benzo[a]pyrene exposure. Do the available human and animal studies support this conclusion?

2c. **Immunotoxicity** (sections 1.1.3, 1.2.1). The draft assessment concludes that immunotoxicity is a potential human hazard of benzo[a]pyrene exposure. Do the available human and animal studies support this conclusion?

2d. **Other types of toxicity** (section 1.1.4). The draft assessment concludes that the evidence does not support other types of noncancer toxicity as a potential human hazard. Are there other types of noncancer toxicity that can be credibly associated with benzo[a]pyrene exposure?

RESPONSE
There are other types of non-cancer toxicity associated with BaP and the EPA review identifies these. However, they appear to be of limited value in determining a NOAEL, LOAEL, or POD for risk assessment.

3. **Dose-response analysis.** In section 2, the draft assessment uses the available human, animal, and mechanistic studies to derive candidate toxicity values for each hazard that is credibly associated with benzo[a]pyrene exposure in section 1, then proposes an overall toxicity value for each route of exposure.

3a. **Oral reference dose for effects other than cancer** (section 2.1). The draft assessment proposes an overall reference dose of $3x10^{-4}$ mg/kg-d based on developmental toxicity during a

critical window of development. Is this value scientifically supported, giving due consideration to the intermediate steps of selecting studies appropriate for dose-response analysis, calculating points of departure, and applying uncertainty factors? Does the discussion of exposure scenarios (section 2.1.5) reflect the scientific considerations that are implicit for exposures during a critical window of development?

RESPONSE

In terms of oral reference dose for non-cancer effects, the EPA report refers to the study by Chen et al. (Chen et al., 2012) as a key study that reflect developmental neurotoxic effects. Chen et al. used the offspring of mated SD rats and tested 10 males and 10 females from different litters. Progeny were treated with 0.02, 0.2, or 2 mg/kg BaP by gavage on P5-11 and the offspring tested for landmark development on P12, 14, 16, and 18, and at later ages in an open-field, elevated plus maze (EPM), and MWM, the later at two ages, P35 and again at P70. Most of the behavioral tests were standard including the EPM which the EPA cited as a particularly noteworthy test because of the effects found. They also noted the importance of the MWM results but also questioned them for reasons outlined above. In brief, in the MWM the authors reported at both P36-39 and P71-74, escape latencies to find the hidden platform were increased in the high dose group. At the adult age, there were also significant latency increases in the mid dose group. On the probe trial, at P40 and P75 there were reduced target quadrant times and reduced numbers of site crossovers were in the high dose group at both ages, and in adults also in the mid dose group. **Weaknesses**: Identified weaknesses detracted from these findings. These included that: (1) size of the MWM was undersized for adult rats; (2) reliance on latency as the sole index of learning; (3) all affected BaP groups showed latency differences from the outset on day-1; (4) no cued trials were given to rule-out visual deficiencies or proximal cue learning deficits; (5) measurements of path length and/or swim speed were not recorded; (6) learning curves were essentially parallel across days showing equal improvement in all group with no evidence that BaP groups ever mastered the task; this affects the interpretation of probe trial differences; and (7) not controlling for multiple comparisons in the data analysis of group differences.

This study also found effects in the EPM at P70 but not at P35. The authors report increased time in open, reduced latency to first open entry, increased number of open arm entries, and decreased entries into closed arms. These effects were seen in the 0.2 and 2 mg/kg BaP groups for latency and time in open at P70 only. On the third measure, number of open arm entries, there were significant increases at P70 in the 2 mg/kg males and in the 0.2 and 2 mg/kg group females. The fourth measure was number of closed arm entries which is complimentary to open arm entries and does not provide unique information. The effects were more prominent in the high dose group than in the mid dose group with no effects in the low dose group. The EPA review identified the EPM effects in this study as key findings, stating that:

> "These results indicate effects on a single, discrete neurological function that are unlikely to be complicated by changes in other processes such as motor activity (total activity, calculated by summing open and closed arm entries was unchanged with treatment). This neurobehavioral endpoint is supported by similar observations in developing (Bouayed et al., 2009a) and adult (Grova et al., 2008) mice, and may be indirectly related to observations of increased aggression in mice (Bouayed et al., 2009b) and is considered adverse."

The difficulty with this interpretation is that the number of open arm entries is the proper measure of activity in this test, not the sum of open and closed arm entries since these are the

converse of one another and essentially measure the same thing, summing them together always results in no difference. Chen et al. found the increase in the number of open arm entries to parallel almost exactly the increase in time in open. The convergence of these two indices is consistently understood in the literature to indicate that increase activity may be a confounding effect driving the increase in time in open. In addition, EPM data are notoriously difficult to replicate. Further, the test can only be used once and for approximately 5 min because once the novelty wears off, it no longer induces the conflict between open and closed spaces to create an approach-avoidance conflict. Furthermore, the test samples only 5 min of behavior and extrapolating from such a snapshot can be influences by many factors such as the animal's handling history, testing conditions and many others. While the test is widely used, it has also been criticized for its limitations. The test remains in use has mostly to do with the lack of alternatives not because the test is regarded as robust. Several alternative methods, including the elevated platform test, have been proposed recently but it is too early to see how they perform. Had Chen et al. found increased time in the open in the absence increased open arm entries, then some limited weight could be placed on the results, but given the potential for confounding in these data this result should not be regarded as 'unlikely to be affected by changes in other processes such as motor activity' rather the opposite is the case. It is this reviewer's recommendation that the EPA not rely on this finding.

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